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ABSTRACT

β_2-Microglobulin has been isolated from several species, but only bovine β_2-microglobulin, previously known as lactollin, has been crystallized. An improved method for its isolation from colostrum is described. The bovine homologue exhibits a concentration-dependent aggregation behavior. β_2-Microglobulin is related to both immune and histocompatibility antigen systems. It exhibits homology with the constant domains of the immunoglobulin-G light and heavy chains and is an integral part of histocompatibility antigens bound to cell surface. β_2-Microglobulin also occurs in the free state in various body fluids including milk and colostrum. The possible relationship of elevated free β_2-microglobulin to pathological conditions is suggested for future research.

INTRODUCTION

β_2-Microglobulin (β_2-μ), a small cell-surface protein (4), is of great interest because it is related structurally to immunoglobulins (9, 26, 34) and is a subunit of histocompatibility antigens (17, 38). It is also free in body fluids (27), including milk and colostrum (6, 16), and is elevated in urine of mammals during renal tubular failure (4, 27). Characterization of β_2-μ from various species should aid in elucidating the precise structural, evolutionary, and functional relationship of this protein to immune and histocompatibility systems. β_2-Microglobulins, indeed, have been isolated from several species, but only the bovine homologue has been crystallized.

This presentation is divided into two main themes, the first covering the general relationship of β_2-μ to immune and histocompatibility antigen systems and the second concentrating on characterization of bovine β_2-μ.

β_2-Microglobulin: Its Relationship to the Immune System

Human β_2-μ first was isolated from urine of patients with chronic cadmium poisoning by Berggard and Bearn in 1968 (4). The protein, 11,800 M_r, contains 100 amino acid residues including two half-cystines involved in a disulfide bond.

β_2-Microglobulin is synthesized by most nucleated cells and is bound to cell surface molecules. It also occurs in free state in various body fluids. For review see Peterson et al. (27). Kithier and Cejka et al. (6, 16) found that in normal serum, β_2-μ averages 1.7 mg/liter compared to 7.2 in fetal sera. The high mean concentration of β_2-μ in human colostrum at delivery is 81.2 mg/liter compared with 23.0 on the 3rd day, which levels off to 13 mg/liter of milk after 2 wk. This concentration for milk is still about 10 times higher than that for normal serum. Free β_2-μ is elevated in body fluids in a number of pathological conditions, which raises the possibility that increased amounts of β_2-μ might serve as a marker for several types of diseases.

The β_2-μ is of special interest because it is related structurally to and shows homology with immunoglobulins as demonstrated by Smithies and Poulik (34), Peterson et al. (26), and Cunningham et al. (9). Figure 1 is a schematic drawing of β_2-μ and the corresponding domains of IgG in which the amino acids are folded into compact units of about 60 residues held together by the -S-S- bond of cystine. They are resistant to proteolysis. Homology between β_2-μ and the C_L, C_H1, C_H2, and C_H3 domains ranges from 21 to 27%. In 1969 Edelman et al. (10) suggested that the immunoglobulin is folded into compact domains stabilized by a single disulfide bond. In 1973, Poljak et al. (30) proved by X-ray crystallography that each domain closely resembles the others in tertiary structure and shares a basic pattern of peptide

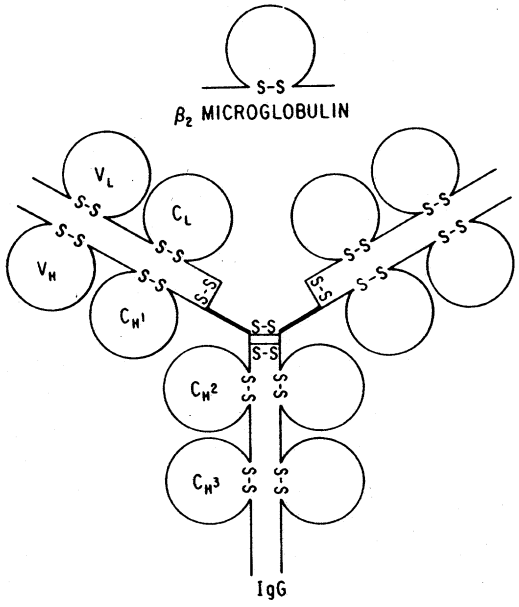


Figure 1. Diagram of β_2-microglobulin and the immunoglobulin molecule, IgG, in which the heavy chain (H) is divided into four homology regions involving variable (V) and constant (C) domains (V_H, C_H1, C_H2, C_H3) and the light chains (L) into two domains (V_L, C_L). The IgG is reproduced from Poljak (29) with his permission.

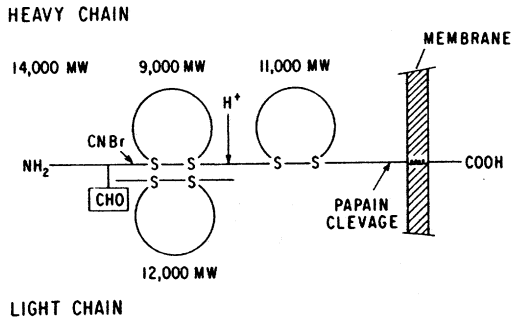


Figure 2. Diagram of histocompatibility antigen. The heavy chain is a modified reproduction from Tragardh et al. (38) with his permission. The light chain is β_2-μ.

chain folding. Now that a crystalline β_2-μ (bovine) is available, the three dimensional structure of this protein can be compared to that of the immunoglobulin domains. Becker et al. (3) published some preliminary data on crystalline bovine β_2-μ.

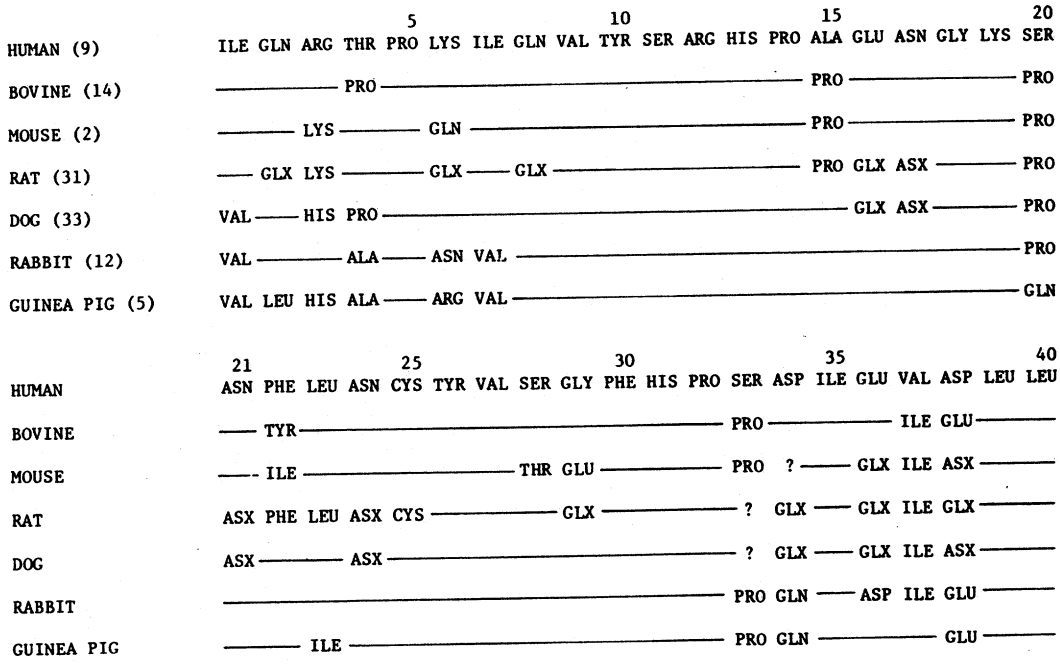
Another important element of the immune system is the major histocompatibility complex, a cluster of genetic loci coding for cell surface glycoproteins (27). This complex codes for antigens which participate in specific biological reactions. Histocompatibility antigens of a graft are recognized by the host as foreign, and after a series of unknown immune reactions, killer lymphocytes are produced which attack the transplant. Hence, they are called transplantation antigens. Histocompatibility antigens also are associated with and appear to regulate many diseases; see Svejgaard and Ryder for a review (36). A significant amount of information on gene mapping of the histocompatibility system is already available for the mouse; attention now has turned to elucidating equivalent data for the human.

Murine histocompatibility antigens are products of chromosome 17 (27). The chromosome region encompassing H-2K to H-2D is called the H-2 complex in which the I and S loci are also. The K and D regions produce the transplantation antigens, the I gene controls immune response antigens, and complement is controlled by the S region. The TL locus, just outside the H-2 complex, controls expression of allotypic variants of certain thymocyte surface antigens. For humans, the HLA complex corresponds to the H-2 complex in mice, and the human transplantation markers are designated A, B, and C while DR codes for the immune response antigens. Characterization of the bovine histocompatibility complex is currently in progress in several laboratories (1, 35, 40).

Figure 2 is a schematic diagram of human histocompatibility antigen. The amino acid sequence of the papain cleaved heavy chain was determined by Peterson's group in Uppsala (38, 39, 41) and Strominger and coworkers at Harvard (17, 21, 25). The amino acid sequences determined by both groups agree. The histocompatibility antigen comprises a heavy chain with a molecular weight of about 44,000. It is anchored through the cell membrane and contains the alloantigenic sites. It is complexed with a light chain of 12,000 M_r, β_2-μ. In contrast to the immunoglobulins the light and heavy chains are not linked covalently. Cleavage of the heavy chain with papain near the cell membrane yields a segment of about 34,000

TABLE 1. Amino acid composition of β_2-microglobulin from various species and of cow lactollin.

	(Residues per mole)						
	β_2-Microglobulin						Lactollin
Amino acid	Human (4)	Guinea pig (7)	Rat (20)	Rabbit (12)	Mouse (22)	Chicken (43)	Cow (13, 14)
Aspartic acid	12	13	10	15	10	14	11
Threonine	5	3	8	4	7	6	2
Serine	10	9	6	6	7	7	8
Glutamic acid	11	10	13	11	11	14	12
Proline	5	7	9	7	8	8	9
Glycine	3	3	2	3	4	7	3
Alanine	2	4	2	2	5	7	1
Half-cystine	2	2	2	2	2	3	2
Valine	7	9	6	10	5	8	5
Methionine	1	1	2	1	4	2	0
Isoleucine	5	5	7	3	6	3	6
Leucine	7	7	6	7	4	7	8
Tyrosine	6	4	4	5	4	3	6
Phenylalanine	5	5	5	5	4	4	4
Lysine	8	8	9	8	9	5	9
Histidine	4	5	4	4	4	1	4
Arginine	5	3	3	4	4	4	5
Tryptophan	2	2	2	2	2	...	2



M_r, which on treatment with cyanogen bromide produces a C-terminal 20,000 peptide and a 14,000 MW N-terminal fragment, the latter containing carbohydrate. The 20,000 dalton peptide is cleaved with acid to yield two fragments of 9,000 and 11,000 M_r, both of which structurally resemble the immunoglobulin domains. Sequence data on the C-terminal 11,000 dalton peptide shows homology with β_2-μ and the constant immunoglobulin domains. The 9,000 and 14,000 M_r peptides do not show amino acid homology to β_2-μ or to the immunoglobulin domains but show a distant relatedness to each other. The immunoglobulin family and at least the 11,000 dalton peptide from the histocompatibility antigen apparently evolved from a precursor gene coding for a protein similar to β_2-μ. For the immunoglobulins this may have occurred through a series of gene duplication events.

Not only have X-ray studies been initiated on crystalline bovine β_2-μ, but examination of the crystal structure of papain cleaved histocompatibility antigen is also in progress (17). The tertiary structure of β_2-μ and the histocompatibility chain should contribute to an understanding of their sites of interaction.

β_2-Microglobulin forms complexes with a number of histocompatibility antigens and with the murine TL antigens. It also is reported to be associated with tumor-specific antigens (37) and is complexed with the H-Y male antigen (11). The H-Y antigen probably has an invariant function in testes induction during embryonic development (24).

Little is known about the actual role of β_2-μ in the immune system. The alloantigenic sites are carried by the histocompatibility antigen heavy chain while the light chain, β_2-μ, is invariant. Lancet et al. (19) suggest that β_2-μ,

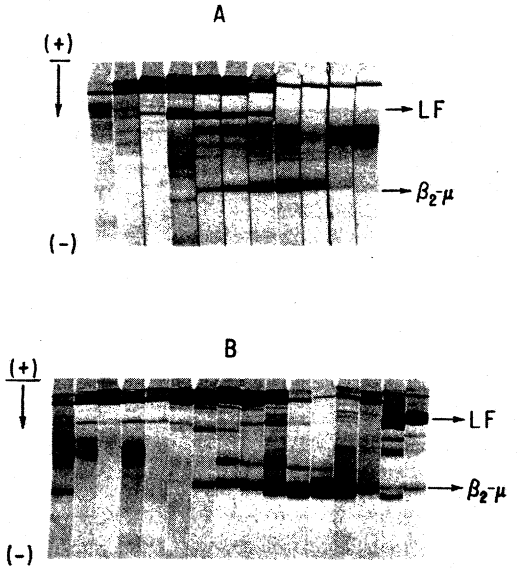


Figure 4. A) Disc gel electrophoretic patterns at pH 4.3, 8 M urea, of fractions of colostrum casein eluted from a DEAE-cellulose column with .005 M sodium phosphate at pH 8.3. The LF indictes lactoferrin. B) Disc gel electrophoretic pattern at pH 4.3, 8 M urea, of fractions eluted from a CM-cellulose column by step-wise elution: .05 M potassium phosphate at pH 5.5 to .2 M potassium chloride in .1 M phosphate buffer, pH 7.7.

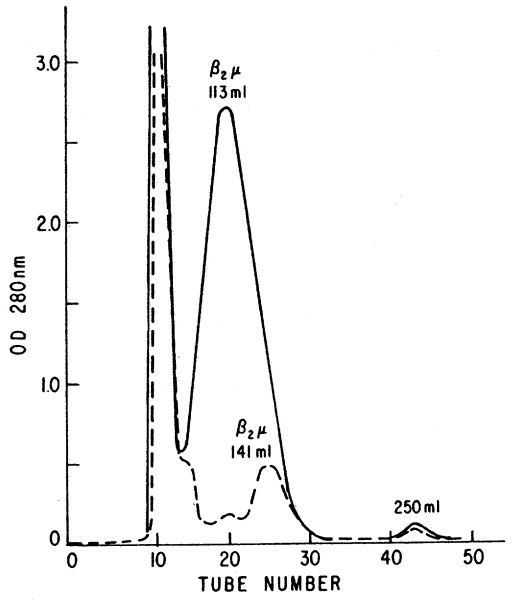


Figure 5. Elution pattern from Bio-Gel P60, .025 M sodium acetate, pH 5.0, 3°C of β_2-microglobulin (β_2-μ) fractions from CM-cellulose. Solid line: 92 mg of 105 mg protein on the column is β_2-μ. Dashed line: 11 mg of 98 mg protein on the column is β_2-μ. The ml indicates total elution volume to peak.

when complexed with the histocompatibility antigen, exhibits a stabilizing effect on the antigen's structure. The β_2-μ may serve an effector function similar to the C_H3 and C_H2 domains of IgG because, like IgG, it binds lymphocyte Fc receptors, a property in which the C_H3 domain of IgG is involved. β_2-Microglobulin also interacts with C1, the first component of complement, a property β_2-μ shares with the C_H2 domain of IgG (27, p. 130). The β_2-μ may play a role in the immune response at the level of T- and B-cell activation as anti-β_2-μ is mitogenic to T- and B-cells (15, 32, 44).

In mastitis, a first response to infection of milk ducts probably is initiated by interaction of bacterial antigen with a few specifically sensitized cells. These sensitized T-cells then elaborate soluble products that amplify cell-mediated immune reactions by affecting activities and production of leucocytes, monocytes, T- and B-cells. In an acute infection, about 95% of the cells in milk are polymorphonuclear leucocytes whereas in chronic mastitis half of the cells are monocytes (macrophage) and T- and B-lymphocytes (23). A disturbing feature of mastitis is that a bacterial attack does not confer immunity to the gland, and a quarter once infected is prone to second infection. Hence, if immunological protection is local, it is either short lived or of little significance. The reason for this lack of protection may be a genetic deficiency related to regulation of the immune response by histocompatability antigens.

The major histocompatibility antigens and β_2-μ should be on the milk fat globule membrane since this membrane is derived principally from plasma membrane of mammary epithelial cells. Wiman et al. (42) demonstrated that human fat globule membrane contains a major amount of the immune response antigen, HLA-DR, and a smaller amount of HLA, A, B, C antigens, including β_2-μ. Using a different method, Plesner and Bjerrum (28) were unable to demonstrate histocompatibility antigens on milk fat globule membranes. This will require further study.

Since the amount of β_2-μ is relatively high in human colostrum and milk compared to that of serum, this also would be expected for cow's milk and colostrum. Cow's colostrum contains more β_2-μ than does normal milk (13); apparently these elevated concentrations in milk and colostrum may be required for the developing calf.

Bovine β_2-Microglobulin

In 1963, we isolated from milk and characterized a new crystalline protein that we called lactollin (13) and reported a molecular weight of about 43,000. Subsequently, we determined that lactollin has a minimum molecular weight of 12,000 based on sodium dodecyl sulfate gel electrophoresis. In 1976, Cunningham and Grey (8) sponsored a symposium on β_2-μ in which the amino acid composition, N-terminal sequence, and molecular weights of β_2-microglobulins from several species were reported. The composition of β_2-microglobulins compared well with that of lactollin (Table 1). This prompted us to investigate the possibility that lactollin was β_2-μ. In all species, tryptophan and half cystine are invariant, with the exception of chicken in which an extra half cystine is reported.

The most convincing evidence that lactollin is β_2-microglobulin is shown by the N-terminal

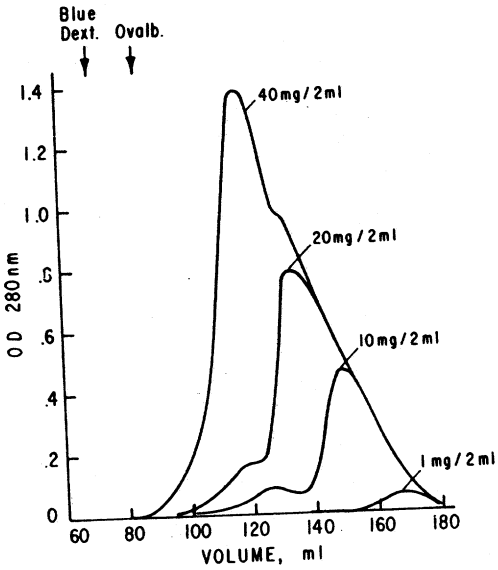


Figure 6. Elution patterns from Bio-Gel P60, .025 M sodium acetate at pH 5.0, 3°C, of pure β_2-microglobulin at different concentrations. Hold up volume is indicated by blue dextran, and the elution peak volume is marked for ovalbumin, 43,000 M_r.

Human β_2-μ has 5 prolines whereas bovine β_2-μ contains 9. The 4 extra prolines occur in the first 33 residues of bovine β_2-μ, and 3 of these substitutions produce prolylproline sequences at residues 4 to 5, 14 to 15, and 32 to 33. In contrast to human β_2-μ, all other β_2-microglobulins also contain at least one prolylproline dipeptide sequence.

Since colostrum is a good source of bovine β_2-μ, we have developed a method for isolating β_2-μ from the casein fraction that precipitates at pH 4.6 from skim colostrum. This consists of four steps: 1) chromatography of colostrum casein on DEAE-cellulose, 2) chromatography of β_2-μ enriched fractions on CM-cellulose, 3) further fractionation of β_2-μ by gel filtration on Bio-Gel P60, and 4) crystallization. Figure 4A shows an analysis by disc gel electrophoresis of fractions of colostrum casein obtained by ion-exchange chromatography. The protein, 24 g, is dissolved in .005 M phosphate buffer at pH 8.3, dialyzed against the same buffer, and applied to a 4 × 50 cm column of DEAE-cellulose. Five grams of protein are eluted with this buffer, and about 3.8 g precipitated when the fractions are acidified to pH 5.0. This precipitate contains no β_2-μ as shown in the first three gels. Lactoferrin begins eluting with β_2-μ whereas β_2-μ continues to elute after lactoferrin is off the column.

The fractions containing β_2-μ from four DEAE-cellulose fractionations are combined, dissolved in .05 M potassium phosphate buffer pH 5.5, and applied to a CM-cellulose column at 3°C, followed by stepwise elution with .1 M potassium phosphate buffer pH 5.5, .1 M potassium chloride in .1 M phosphate buffer pH 5.5, and .2 M potassium chloride in .1 M phosphate buffer pH 7.7. Figure 4B shows the disc gel electrophoretic patterns of the eluted fractions. The first gel shows an analysis of the small amount of protein which is insoluble in buffer at pH 5.5 and indicates β_2-μ, presumably complexed with insoluble proteins. About 2.5 g of protein contains no β_2-μ as shown by gels 2 to 6 while the balance of eluted proteins representing .6 g contains β_2-μ. In contrast to separation on DEAE cellulose, most of the β_2-μ is eluted from CM-cellulose before lactoferrin. Recently, we found that a salt gradient is more efficient in eluting β_2-μ in a narrower range of tubes.

Protein fractions from CM-cellulose next were dissolved in .025 M sodium acetate at pH 5.0 and subjected to gel filtration on Bio-Gel, P60 at 3°C. Figure 5 shows elution profiles of two experiments in which β_2-μ is in large and small amounts relative to the total protein applied to the column. The peak elution volume is different for the two chromatograms, indicating that β_2-μ self associates with increasing concentration. Figure 6 shows further evidence of the concentration-dependent aggregation of β_2-μ in which several concentrations of pure β_2-μ are chromatographed on a Bio-Gel P60 column. Guinea pig β_2-μ shows a similar phenomenon (7). Apparently, human β_2-μ does not associate since it has the same sedimentation coefficient of 1.65 from .1 to 1.1% concentration (4).

The final purification of β_2-μ is by crystallization. The protein is dissolved at pH 5, and when the pH is increased slowly to 8, the solution becomes turbid, then strongly birefringent, and after a few days at 3°C, β_2-μ crystals are harvested by centrifugation. About 1 mg β_2-μ is obtained from 1 g of colostrum casein. Figure 7 shows the crystalline form of β_2-μ.

The physical chemical properties of bovine β_2-μ are now under investigation at this Center. At β_2-μ concentrations of less than .05%, pH 5.0, an 11,800 M_r is obtained by sedimentation equilibrium (18). At concentrations above .1%, both sedimentation equilibrium and velocity show a limited reversible self association to a tetramer. The β_2-μ also undergoes an irreversible temperature dependent association to a much larger aggregate over several days.

Bovine β_2-μ is the only species of this protein that has been crystallized. Crystallographic data on β_2-μ will be the final proof of whether the immunoglobulin domains and β_2-μ have the same type of folding in their tertiary structures.

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